

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

SWANSON, Barry, J.
Swanson & Bratschun, L.L.C.
Suite 330
1745 Shea Center Drive
Highlands Ranch, CO 80129
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 16 janvier 2002 (16.01.02)	
Applicant's or agent's file reference NEX 87/PCT	IMPORTANT NOTIFICATION
International application No. PCT/US00/20397	International filing date (day/month/year) 26 juillet 2000 (26.07.00)

1. The following indications appeared on record concerning: <input checked="" type="checkbox"/> the applicant <input type="checkbox"/> the inventor <input type="checkbox"/> the agent <input type="checkbox"/> the common representative		
Name and Address NEXSTAR PHARMACEUTICALS, INC. Suite 200 2860 Wilderness Place Boulder, CO 80301 United States of America	State of Nationality US	State of Residence US
Telephone No. _____		
Facsimile No. _____		
Teleprinter No. _____		
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: <input checked="" type="checkbox"/> the person <input type="checkbox"/> the name <input type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence		
Name and Address GILEAD SCIENCES, INC. 333 Lakeside Drive Foster City, CA 94404 United States of America	State of Nationality US	State of Residence US
Telephone No. _____		
Facsimile No. _____		
Teleprinter No. _____		
3. Further observations, if necessary: _____ _____ _____		
4. A copy of this notification has been sent to: <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input type="checkbox"/> the International Preliminary Examining Authority </div> <div> <input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other: _____ </div> </div>		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Yukari NAKAMURA Telephone No.: (41-22) 338.83.38
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INTERNATIONAL PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year)
18 June 2001 (18.06.01)

International application No.
PCT/US00/20397

Applicant's or agent's file reference
NEX 87/PCT

International filing date (day/month/year)
26 July 2000 (26.07.00)

Priority date (day/month/year)
29 July 1999 (29.07.99)

Applicant

PAGRATIS, Nikos et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
16 February 2001 (16.02.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Maria Kirchner

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

REC'D 15 MAY 2001

WIPO

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference NEX 87/PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/410)	
International application No. PCT/US00/20397	International filing date (day/month/year) 26 JULY 2000	Priority date (day/month/year) 29 JULY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): C07H 21/02, 21/04 and US Cl.: 556/22.1		
Applicant NEXSTAR PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 3 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 16 FEBRUARY 2001	Date of completion of this report 23 APRIL 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  STEPHANIE ZITOMER, PHD
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/20397

I. Basis of the report**1. With regard to the elements of the international application:***☒ the international application as originally filed☒ the description:

pages 1-81 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the claims:

pages 82 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the drawings:

pages 1-13 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the sequence listing part of the description:

pages 1-81 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in printed form.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/fig NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/20397

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims	<u>1-8</u>	YES
	Claims	<u>NONE</u>	NO
Inventive Step (IS)	Claims	<u>1-8</u>	YES
	Claims	<u>NONE</u>	NO
Industrial Applicability (IA)	Claims	<u>1-8</u>	YES
	Claims	<u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-8 meet the criteria for novelty and inventive step set out in PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest the claimed invention nucleic acid ligand to TGFbeta2 selected from the group consisting of disclosed nucleotide sequences (claim 1) or the claimed invention complex comprised of a TGFbeta2 nucleic acid ligand and a non-immunogenic, high molecular weight (NIHMW) compound or a lipophilic compound (claim 2) including embodiments comprising a linker between the ligand of claim 2 and the NIHMW or lipophilic compound (claim 3); the NIHMW compound is a polyalkylene glycol (claim 4); which may be polyethylene glycol (claim 5) having a molecular weight of about 10-80 K (claim 6) or about 20-45 K (claim 7) or the specific nucleic acid ligand and chemical structure of claim 8. Toothman et al. (5,731,228) disclose a nucleic acid ligand to TGFbeta1, a compound related to but different in structure and function from, TGFbeta2. Janjic et al. (5,731,424) disclose a complex of a nucleic acid ligand to VEGF and a NIHMW compound or a lipophilic compound and provide background teachings on the subject of complexing nucleic acid ligands with NIHMW and lipophilic compounds. The skilled practitioner in the art would not have been motivated to combine the reference teachings due to lack of overlap of subject matter especially with regard to the different physiological roles of VEGF and TGFbeta1. VEGF is a stimulator of endothelial cells and is involved in angiogenesis whereas TGFbeta polypeptides primarily influence growth, differentiation and gene expression in cells.

Claims 1-8 meet the criteria for industrial applicability set out in PCT Article 33(4), because the skilled practitioner in the art would have recognized that the utility of TGFbeta2 nucleic acid ligands and complexes for diagnostic and therapeutic applications would be essentially the same as that of VEGF ligands and complexes as taught by Janjic et al.

____ NEW CITATIONS _____
NONE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20397

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 21/02, 21/04

US CL : 536/22.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/22.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, DIALOG ONESEARCH; search terms: nucleic ligand, aptamer, TGFbeta2, polyethylene glycol, lipophilic, nonimmunogenic, polyalkylene glycol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,731,424 A (TOOTHMAN et al.) 24 March 1998, claims 1-9; col. 5, line 66-col. 6, line 1.	2-7
Y	US 5,859,228 A (JANJIC et al.) 12 January 1999; see entire document.	2-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 26 OCTOBER 2000	Date of mailing of the international search report 24 NOV 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer STEPHANIE ZITOMER, PHD Telephone No. (703) 308-0196